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Combined effect of glutathione *S*-transferase M1 and T1 genotypes on bladder cancer risk

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Abstract

To evaluate the association between genetic polymorphism of *GSTM1, GSTT1* and development of bladder cancer, a hospital-based case-control study was conducted in South Korea. The study population consisted of 232 histologically confirmed male bladder cancer cases and 165 male controls enrolled from urology departments with no previous history of cancer or systemic diseases in Seoul during 1997–1999. The *GSTM1* null genotype was significantly associated with bladder cancer (OR: 1.6, 95% CI: 1.0–2.4), whereas the association observed for *GSTT1* null genotype did not reach statistical significance (OR: 1.3, 95% CI: 0.9–2.0). There was a statistically significant multiple interaction between *GSTM1* and *GSTT1* genotype for risk of bladder cancer ($P = 0.04$); the risk associated with the concurrent lack of both of the genes (OR: 2.2, 95% CI: 1.2–4.3) was greater than the product of risk in men with *GSTM1* null/*GSTT1* present (OR: 1.3, 95% CI: 0.7–2.5) or *GSTM1* present/*GSTT1* null (OR: 1.1, 95% CI: 0.6–2.2) genotype combinations.

Keywords: *GSTM1*; *GSTT1*; Combined effect; Genetic polymorphisms; Bladder cancer

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1. Introduction

Bladder cancer ranks fourth in incidence of cancer in the United States [1]. Its incidence among non-Hispanic white men in US was 33.1/100 000 in 1988–1992 [1], which is similar to that found in most European countries [2]. In contrast, the incidence of bladder cancer appears to be much lower in Korean men, being 7.8/100 000 in 1989 [3]. These differences may be explained by environmental or dietary factors or by genetic backgrounds. A large difference also exists between sexes in both countries; this malignancy is three to four times more frequent in men than in women [1,3].

Exposure to chemicals in tobacco smoke and other environmental and occupational chemicals has been described as risk factors for bladder cancer in numerous epidemiological and laboratory studies (e.g. 2-naphthylamine, benzidine, 4-aminobiphenyl) [1,4]. Genetic differences in the metabolism of these chemicals have been recently suggested as modifiers of individual susceptibility to environmentally-induced bladder cancer. Glutathione *S*-transferases (GSTs) detoxify reactive chemical species, such as polycyclic aromatic hydrocarbon (PAH) epoxides present in tobacco smoke, by conjugating them with glutathione. The *GST* multigene family consists of at least four enzyme classes: the alpha, mu, theta, and pi with partially overlapping substrate specificities [5].

Subsequent to the first report by Bell et al. [6] that *GSTM1* deficiency increased risk of bladder cancer in a hospital-based case control study, a number of studies appeared with supporting findings [7–14]. In contrast to *GSTM1*, studies exploring the potential role of *GSTT1* genotype in individual susceptibility to bladder cancer have reported inconsistent results. A few studies showed non-significantly decreased risk of bladder cancer with *GSTT1* null genotype [15–17], whereas others showed increased bladder cancer risk with *GSTT1* null genotype [13,18]. Inconsistent results have also emerged from the recent studies exploring the potential combined effect of *GSTM1* and *GSTT1* genotypes in development of this malignancy [13,16,19,20].

In this study, the potential role of *GSTM1* and *GSTT1* genotypes in bladder cancer risk was examined further in a Korean study population.

2. Methods

2.1. Study subjects and selection

The study population consisted of 232 histologically confirmed male bladder cancer cases admitted for treatment to urology departments of three teaching hospitals in Seoul during February 1997–May 1999 (Seoul National University Hospital, Boramae Hospital, and Samsung Medical Center) and 165 male controls with no present or previous history of cancer or systemic illnesses admitted to the same departments. Approximately 95% of cases diagnosed at these hospitals were asked to participate in the study. Approximately 8% of cases and 17% of controls approached were not included in the final study population because of refusal to participate in the study, failure to be interviewed, and/or because no blood samples were available for them. Among 204 bladder cancer cases for whom information on the number of months from diagnosis to interview was available, the median was 10.5 months. A total of 101 cases had no previous tumor resection. The controls were selected from the same urology departments in the same hospitals using the following criteria: (1) they had no current or previous cancer or systemic disease; and (2) they were over 40 years old males. Thirty six percent of controls had benign prostate hypertrophy (BPH), 16% had kidney or ureter stones, 9% had urethral stricture, 5% had hydrocele, and 5% had urethral infections. The remaining 27% had other disorders that included kidney rupture, obstructive uropathy, scrotal swelling, erection disorder, penile foreign body, or kidney donor. All study subjects provided informed consent prior to participating in the study. Information on demographic characteristics (education, marital status, weight, height, etc.), usual occupation and history of ever-working at previously identified high risk industries [4,21], lifestyle habits including smoking (if they had smoked more than 400 cigarettes in their life time, current status of smoking, duration of smoking, amount of cigarettes consumed per day, etc.), alcohol consumption (never, social, heavy, etc.), and history of urinary tract stones and tuberculosis was collected by trained interviewer with a standardized questionnaire. The study was approved by the institutional review board of Seoul National University Hospital.

2.2. DNA extraction

Blood was collected in 10 ml heparinized tubes and centrifuged at 3000 rpm for 10 min at room temperature within 10 h of collection. Plasma, buffy coat, and red blood cells were separated and stored at −70°C. The buffy coat (0.5–1 ml) was kept frozen until it was thawed for DNA extraction for this study. DNA was isolated from these buffy coat samples with an Applied QIAGEN extraction kit using protocols and reagents supplied (Chatsworth, CA, USA). The extracted DNA was stored at −20°C until the genotype analyses.

2.3. Genotyping analyses

The *GSTM1* and *GSTT1* genotypes were determined essentially as described earlier [6,22,23]. Briefly, the β-globin specific primer pair (B1: 5′-caa-ctt-cat-cca-cgt-tca-cc-3′ and B2: 5′-gaa-gac-cca-agg-aca-ggt-ac-3′) was used together with the *GSTM1* specific primer pair (G5: 5′-gaa ctc cct gaa aag cta aag c-3′, G6: 5′-gtt ggg ctc aaa tat acg gtg g-3′) and the *GSTT1* specific primer pair (Tf: 5′-ttc ctt act ggt cct cac atc tc-3′, Tr: 5′-tca ccg gat cat ggc cag ca-3′) in a multiplex PCR reaction. The PCR was carried out in a total volume of 50 μl, containing 5 μl of DNA template (50–100 ng), 50 pmole of each of the above primers, and 1.25 units of Taq polymerase (Perkin-Elmer, USA). The reaction was incubated at 94°C for 4 min, prior to 30 cycles of denaturation of 20 s at 94°C, annealing of 20 s at 57°C, and extension of 45 s at 72°C (45 s), followed by a final extension of 5 min at 72°C. Subsequent to PCR, an 10 μl aliquot was run on a 3% Metaphor agarose gel (FMC BioProducts, USA) in ethidium bromide stained TAE buffer (50 Volt, 1 h), after which the bands were visualized and photographed under UV transillumination. The internal standard fragment amplified from β-globin was 268 bp of length, whereas presence of the *GSTM1* and *GSTT1* genes was identified by 210 and 480 bp fragments, respectively. Forty samples were independently re-analyzed by our Finnish collaborators to evaluate the assay reliability; complete agreement was observed between the results from the Finnish and Korean laboratories.

2.4. Statistical analyses

To examine the associations between known or suspected risk factors and bladder cancer, and between the *GSTM1* and *GSTT1* genotypes and bladder cancer risk, odds ratios (ORs) and 95% confidence intervals (CIs) were calculated by unconditional logistic regression [24]. The ORs were adjusted for age and smoking. The multiple interaction between *GSTM1* and *GSTT1* genotypes on bladder cancer risk was evaluated by adding the new product variable [gstm1 genotype] × [gstt1 genotype] in the logistic regression model. The product variable between genotypes and smoking [gst genotype] × [pack-year group] was also added in the logistic model when evaluating the interactive effect of *GST* genotypes and smoking on bladder cancer risk.

3. Results

Selected characteristics of bladder cancer cases and controls are presented in Table 1. The mean age of bladder cancer patients and controls was 63.9 years (SD 10.6 years) and 62.8 years (SD 12.1 years), respectively. There was a statistically significant dose-dependent increase in risk of bladder cancer associated with smoking (P for trend = 0.009). Although a slightly higher percentage of cases than controls had ever worked in high-risk occupations (31 and 27%, respectively), no significant differences were observed between these groups in any of the other variables tested.

The distribution of *GST* genotypes and risk of bladder cancer are shown in Table 2. The observed frequencies of *GSTM1* and *GSTT1* null genotypes in controls (52 and 58%, respectively) are similar to those previously observed in Asians [16].

The *GSTM1* null genotype was significantly associated with increased risk of bladder cancer (OR: 1.6, 95% CI: 1.0–2.4). A tendency of increased risk was also observed between *GSTT1* null genotype and bladder cancer, but this association failed to reach statistical significance (OR: 1.3, 95% CI: 0.9–2.0) (Table 2). When incident and prevalent cases were examined separately the results were similar for both subgroups and no significant differences were seen in these results compared with those for the total case group (Table 2).

The *GSTM1* null genotype frequency was not statistically different between various subgroups of cases;: the frequency was 55% ($n = 59$, 95% CI: 42–68) among primary cases diagnosed less than 12 months

Table 1
Selected characteristics for 232 bladder cancer cases and 165 controls subjects[a]

Characteristics	Cases		Controls		*P*-value/OR (95% CI)
	N	(%)	*N*	(%)	
Age					
Under 49	23	10.0	27	16.4	
50–59	41	17.7	32	19.4	
60–69	99	42.7	49	29.7	0.65 (chi square)
70–79	54	23.3	34	20.6	
Over 80	11	4.7	14	8.5	
Missing	4	1.7	9	5.5	
Mean age (SD)	63.9	(10.6)	62.8	(12.1)	0.36 (*t*-test)
Education					
Under high school	52	22.4	42	25.4	
At and over high school	97	41.8	52	31.5	0.32 (chi square)
Missing	83	35.8	71	43.0	
*Smoking**					
Non-smokers	32	13.8	29	17.6	1.0 (reference)
1–30 pack-years	83	35.8	57	34.5	1.3 (0.7–2.4)
> 30 pack years	88	37.9	36	21.8	2.2 (1.2–4.2)
Missing	29	12.5	43	26.1	
Mean pack-years (SD)	30.5	(33.4)	23.7	(25.5)	0.04 (*t*-test)
Alcohol consumption					
Never	85	36.6	59	35.8	
Social	71	30.6	53	32.1	0.53 (chi square)
Heavy	49	21.1	26	15.8	
Missing	27	11.6	27	16.4	
*High risk occupation***					
No	133	57.3	91	55.2	0.29 (chi square)
Yes	71	30.6	45	27.3	
Missing	28	12.1	29	17.6	

[a] **P* for trend = 0.009; and ***high risk occupation was defined as positive history of ever-working at the presumed high risk industries (dye, rubber, leather, aluminum, paint, tire manufacturing, petrochemical industry, etc.). The ORs were adjusted for age.

before interview, 72% ($n = 29$, 95% CI: 56–88) among primary cases diagnosed more than 12 months before interview, 61 % ($n = 33$, 95% CI: 47–78) among recurrent cases diagnosed less than 12 months before interview, and 66% ($n = 50$, 95% CI: 53–79) among recurrent cases diagnosed more than 12 months before interview (chi square = 3.1, $P = 0.38$). Neither was the *GSTM1* null genotype frequency statistically different between lower and higher grade or stage of diseases (data not shown). Similarly to *GSTM1* null genotype, the frequency of the *GSTT1* null genotype frequency did not significantly differ between various subgroups of cases (data not shown).

There was a statistically significant multiple interaction between *GSTM1* and *GSTT1* genotypes in risk of bladder cancer (P for interaction = 0.04); concurrent lack of both *GST* genes posed a 2.2-fold risk (95% CI: 1.2–4.3) of bladder cancer compared to the presence of both genes (Table 3). The risk was greater than the product of risk in men with *GSTM1* null/*GSTT1* present (OR: 1.3, 95% CI: 0.7–2.5) or *GSTM1* present/*GSTT1* null (OR: 1.1, 95% CI: 0.6–2.2) genotype combinations (Table 3).

There was, no evidence of a multiple interaction between either *GSTM1* or *GSTT1* genotypes and smoking (Table 4).

4. Discussion

We observed an increased risk for bladder cancer associated with the *GSTM1* null genotype, in agree-

Table 2
Genotype frequency of *GSTM1* and *GSTT1* and association between combination of genotypes and bladder cancer[a]

	Controls		All cases			Incident cases			Prevalent cases		
	N	%	*N*	%	OR (95% CI)**	*N*	%	OR (95% CI)**	*N*	%	OR (95% CI)**
GSTM1											
Present	79	47.9	83	35.8	1.0 (reference)	43	38.1	1.0 (reference)	30	33.0	1.0 (reference)
Null	86	52.1	149	64.2	1.6 (1.0–2.4)	70	61.9	1.4 (0.9–2.3)	61	67.0	1.8 (1.0–3.0)
GSTT1											
Present	80	48.5	97	41.8	1.0 (reference)	45	39.8	1.0 (reference)	38	41.8	1.0 (reference)
Null	85	51.5	135	58.2	1.3 (0.9–2.0)	68	60.2	1.5 (0.9–2.4)	53	58.2	1.3 (0.8–2.2)
Combination of GSTM1 and GSTT1											
Both present	31	18.8	31	13.4	1.0 (reference)	14	12.4	1.0 (reference)	10	11.0	1.0 (reference)
Either null	97	58.8	118	50.9	1.2 (0.7–2.2)	60	53.1	1.3 (0.6–2.7)	48	52.7	1.5 (0.7–3.4)
Both null	37	22.4	83	35.8	2.2 (1.2–4.2)	39	34.5	2.2 (1.0–4.9)	33	36.3	2.7 (1.1–6.3)
			P for trend = 0.010			*P* for trend = 0.030			*P* for trend = 0.018		

[a] OR: odds ratio, 95% CI: 95% confidence interval of odds ratio. *Incident cases defined as diagnosed within 12 months whereas prevalent cases defined as diagnosed more than 12 months. **The ORs were adjusted for age and smoking (non-smokers, 1–30 pack-years, >30 pack-years).

ment with several previous studies (summarized in [25–27]). A tendency of increased risk was also observed for the *GSTT1* null genotype (OR: 1.3, 95% CI: 0.9–2.3), although this difference was not statistically significant. Our findings agree with two previous studies, one of which showed a significantly increased risk (OR: 2.1, 95% CI: 1.1–3.9) for the *GSTT1* null genotype [13], and the other a non-significantly increased risk for *GSTT1* null genotype [19]. Three other studies, however, showed a non-significantly decreased risk for the *GSTT1* null genotype [15,16,20].

Concurrent lack of both *GSTM1* and *GSTT1* genes posed more than a 2-fold risk of bladder cancer (OR: 2.2, 95% CI: 1.2–4.3) compared to the presence of both of the genes (*P* for interaction = 0.04). This is suggestive of a synergistic function between *GSTM1* and *GSTT1* genotypes in the etiology of bladder cancer. Although one of the previous studies [28] found a similar significant interactive effect between the *GSTM1* and *GSTT1* genotypes in bladder cancer proneness (OR: 9.9, 95% CI: 1.8–46.9), no interactive effects were observed in several recent reports [16,19,20].

Table 3
ORs and 95% CIs for interaction between *GSTM1* and *GSTT1* genotypes and bladder cancer risk[a]

	GSTM1 present (cases/controls)	*GSTM1* null (cases/controls)
GSTT1 present	1.0 (31/31)	1.3 (0.7–2.5) (66/49)
GSTT1 null	1.1 (0.6–2.2) (52/48)	2.2 (1.2–4.3) (83/37)

[a] The ORs were adjusted for age in the logistic model. *P* for interaction = 0.04.

The present findings are consistent with the results from laboratory studies on the functional role of *GSTM1* and *GSTT1* in bladder carcinogenesis; *GSTM1* is involved in conjugating reactive species of known bladder carcinogens like PAHs present in tobacco smoke, whereas no known bladder carcinogens have been identified as substrates for *GSTT1*. However, since no association between *GST* genotype and tobacco use was observed in this study, the *GST* genotype may play a role in bladder carcinogenesis irrespective of carcinogen exposure. A larger study is needed to confirm the interactive effect of *GST* genotype and carcinogen exposure on bladder carcinogenesis.

The main limitation of this study was that it included cases diagnosed greater than 12 months and/or cases with recurrent tumor development. Therefore, although the genotype frequencies were not significantly different across case subgroups, a larger study of newly diagnosed primary cases in the same populations is needed to verify the present findings.

Table 4
ORs and 95% CIs for interaction between *GST* genotypes and smoking[a]

	*GSTM1**		*GSTT1***	
	Present (cases/controls)	Null (cases/controls)	Present (cases/controls)	Null (cases/controls)
Smoking status				
Non-smokers	1.0 (11/15)	2.0 (0.7–5.7) (21/14)	1.0 (15/15)	1.2 (0.4–3.3) (17/14)
1–30 pack-years	1.8 (0.7–4.6) (30/23)	2.1 (0.9–5.2) (53/34)	1.6 (0.6–3.7) (39/25)	1.4 (0.6–3.2) (44/32)
> 30 pack-years	2.6 (1.0–6.9) (35/18)	4.0 (1.6–10.3) (53/18)	2.1 (0.8–5.2) (33/16)	2.8 (1.1–6.6) (55/20)
P for trend	0.05	0.08	0.13	0.04

[a] The ORs were adjusted for age in the logistic model. **P* for interaction = 0.07; and ***P* for interaction = 0.16.

In conclusion, these results support the hypothesis that the *GSTM1* null genotype may be associated with increased risk of bladder cancer in men, and that the effect may be greater in the presence of the *GSTT1* null genotype.

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References

[1] D.T. Silverman, N. Rothman, S.S. Devesa, Epidemiology of bladder cancer, in: K.N. Syrigos, D.G. Skinner (Eds.), Bladder Cancer. Biology, Diagnosis, Management, Oxford University Press, Inc., New York, 1999, pp. 11–55.

[2] E. Negri, C.L. Vechia, Epidemiology and prevention of bladder cancer, Eur. J. Cancer Prev. 10 (2001) 7–14.

[3] C.W. Lee, E.S. Lee, H. Choi, S.K. Koh, J.M. Lee, S.E. Chai, B.K. Min, S.C. Lee, J.B. Yoon, Y.H. Koh, Incidence estimation of genitourinary cancer in Korea, J. Korean Med. Sci. 7 (2) (1992) 154–161.

[4] P. Vineis, L. Simonato, Proportion of lung and bladder cancers in males resulting from occupation, Arch. Environ. Health 46 (1991) 6–15.

[5] J.D. Hayes, D.J. Pulford, The glutathione *S*-transferase supergene family: regulation of *GST* and the contribution of the isoenzymes to cancer chemoprevention and drug resistance, Crit. Rev. Biochem. Mol. Biol. 30 (6) (1995) 445–600.

[6] D.A. Bell, J.A. Taylor, D.F. Paulson, C.N. Robertson, J.L. Mohler, G.W. Lucier, Genetic risk and carcinogen exposure: a common inherited defect of the carcinogen-metabolism gene glutathione *S*-transferase M1 (*GSTM1*) that increases susceptibility to bladder cancer, J. Natl. Cancer Inst. 85 (1993) 159–164.

[7] J. Brockmöller, R. Kerb, N. Drakoulis, B. Staffeldt, I. Roots, Glutathione *S*-transferase M1 and its variant A and B as host factors of bladder cancer susceptibility: a case-control study, Cancer Res. 54 (1994) 4103–4111.

[8] A.K. Daly, D.J. Thomas, J. Cooper, W.R. Pearson, D.E. Neal, J.R. Idle, Homozygous deletion of gene for glutathione *S*-transferase M1 in bladder cancer, Br. Med. J. 307 (1993) 481–482.

[9] T. Katoh, H. Inatomi, A. Nagaoka, A. Sugita, Cytochrome P4501A1 gene polymorphism and homozygous deletion of the glutathione *S*-transferase M1 gene in urothelial cancer patients, Carcinogenesis 16 (1995) 655–657.

[10] H.J. Lin, C.Y. Han, D.A. Bernstein, W. Hsiao, B.K. Lin, S. Hardy, Ethnic distribution of the glutathione transferase Mu 1-1 (*GSTM1*) null genotype in 1473 individuals and application to bladder cancer susceptibility, Carcinogenesis 15 (5) (1994) 1077–1081.

[11] N.A. Mungan, K.K. Aben, E. Beeks, E. Kampman, A. Bunschoten, M. Bussemakers, J.A. Witjes, L.A. Kiemeney, A germline homozygote deletion of the glutathione-*S*-transferase Mu1 gene predisposes to bladder cancer, Urol. Int. 64 (3) (2000) 134–138.

[12] H. Okkels, T. Sigsgaard, H. Wolf, H. Autrup, Glutathione *S*-transferase μ as a risk factor in bladder tumors, Pharmacogenetics 6 (1996) 251–256.

[13] J. Salagovic, I. Kalina, J. Stubna, V. Habalova, M. Hrivnak, L. Vlansky, A. Kohut, E. Biros, Genetic polymorphism of glutathione *S*-transferases M1 and T1 as risk factor in lung and bladder cancer, Neoplasma 45 (5) (1998) 312–317.

[14] S. Zhong, A.H. Wyllie, D. Barnes, C.R. Wolf, N.K. Spurr, Relationship between the *GSTM1* genetic polymorphism and

susceptibility to bladder, breast and colon cancer, Carcinogenesis 14 (9) (1993) 1821–1824.
[15] J. Brockmöller, I. Cascorbi, R. Kerb, I. Roots, Combined analysis of inherited polymorphisms in arylamine *N*-acetyltransferase 2, glutathione *S*-transferases M1 and T1, microsomal epoxide hydrolase, and cyctochrome P450 enzymes as modulators of bladder cancer risk, Cancer Res. 56 (1996) 3915–3925.
[16] T. Katoh, H. Inatomi, H. Kim, M. Yang, T. Matsumoto, T. Kawamoto, Effects of glutathione *S*-transferase (*GST*) M1 and *GSTT1* genotypes on urothelial cancer risk, Cancer Lett. 132 (1998) 147–152.
[17] M. Kempkes, K. Golka, S. Reich, T. Reckwitz, H.M. Bolt, Glutathione *S*-transferase *GSTM1* and *GSTT1* null genotypes as potential risk factors for urothelial cancer of bladder, Arch. Toxicol. 71 (1996) 123–126.
[18] S.J. Lee, D. Kang, S.H. Cho, S.U. Kim, M.S. Park, H.Y. Choi, H. Choi, Association of genetic polymorphism of glutathione *S*-transferase M1 and T1 and bladder cancer, J. Korean Cancer Assoc. 31 (3) (1999) 548–555.
[19] I. Georgiou, I.F. Filiadis, Y. Alamanos, I. Bouba, X. Giannakopoulos, D. Lolis, Glutahione *S*-transferase null genotypes in transitional cell bladder cancer. A case-control study, Eur. Urol. 37 (6) (2000) 660–664.
[20] W.J. Kim, H.L. Lee, S.C. Lee, Y.T. Kim, H. Kim, Polysmorphisms of *N*-acetyltransferase 2, glutathione *S*-transferase mu and theta genes as risk factors of bladder cancer in relation to asthma and tuberculosis, J. Urol. 164 (1) (2000) 209–213.
[21] D.T. Silverman, L.I. Levin, R.N. Hoover, P. Hartge, Occupational risks of bladder cancer in the United States, J. Natl. Cancer Inst. 81 (1989) 1472–1480.
[22] H. Chen, D.P. Sandler, J.A. Talyor, D.L. Shore, E. Liu, C.D. Bloomfield, D.A. Bell, Increased risk for myelodysplastic syndromes among those with glutathione transferase theta 1 (*GSTT1*) gene defect, Lancet 347 (1996) 195–197.
[23] S. Pemble, K.R. Schroeder, S.R. Spencer, D.J. Meyer, E. Hallier, H.M. Bolt, B. Ketterer, B. Taylor, Human glutathione *S*-transferase theta (*GSTT1*): cDNA cloning and the characterization of a genetic polymorphism, Biochem. J. 300 (1994) 271–276.
[24] N.E. Breslow, N.E. Day, Statistical Methods in Cancer Research. The Analysis of Case-Control Studies, 1, IARC Scientific Publications No. 32, Lyon, 1980.
[25] J. Brockmöller, I. Cascorbi, R. Kerb, C. Sachse, I. Roots, Polymorphisms in xenobiotic conjugation and disease predisposition, Toxicol. Lett. 102–103 (1998) 173–183.
[26] A. d'Errico, E. Taioli, X. Chen, P. Vines, Genetic metabolic polymorphisms and the risk of cancer: a review of the literature, Biomarkers 1 (1996) 149–173.
[27] T.R. Rebbeck, Molecular epidemiology of the human glutahione *S*-transferase genotypes *GSTM1* and *GSTT1* in cancer susceptibility, Cancer Epidemiol. Biomarkers Prev. 6 (1997) 733–743.
[28] S.Z. Abdel-Rahman, W.A. Anwar, W.E. Abdel-Aal, H.M. Mostafa, W.W. Au, *GSTM1* and *GSTT1* genes are potential risk modifiers for bladder cancer, Cancer Detect. Prev. 22 (2) (1998) 129–138.